UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

MERCK SHARP & DOHME CORP., *Plaintiff*, v. ACTAVIS LABORATORIES FL, INC., ANDRX CORPORATION, ACTAVIS PHARMA, INC. AND ACTAVIS, INC., *Defendants.*	)	Civil Action No: 15-cv-6075 (PGS)(DEA) **MEMORANDUM AND ORDER**

SHERIDAN, U.S.D.J.

This is a patent infringement action brought by Merck Sharp & Dohme Corp. ("Merck" or "Plaintiffs") against Actavis Laboratories FL, Inc., Andrx Corporation, Actavis Pharma, Inc. and Actavis, Inc. (collectively, "Actavis" or "Defendants") for filing an Abbreviated New Drug Application ("ANDA") with the Food & Drug Administration ("FDA"), pursuant to 21 U.S.C. § 355(b)(2), for approval to engage in the commercial manufacture, use or sale of a generic version of Merck's Noxafil® (posaconazole). *See* 35 U.S.C. § 271(e)(2).

Merck listed the U.S. Patent No. 5,661,151 ("the '151 patent") with the FDA's Approved Drug Products with Therapeutic Equivalence Applications, commonly known as the Orange Book, in order to market and sell a generic version of Noxafil®. *See* 21 U.S.C. § 355(b)(1). The '151 patent is directed to the synthesis and clinical use of the antifungal compound posaconazole, which is used for treating or preventing fungal infections.

Merck alleges that by filing the ANDA application with the FDA, and in particular making a Paragraph IV certification with their filing, Actavis had indicated that Merck's '151 patent is

"invalid or will not be infringed by the manufacture, use, or sale of [Actavis'] new drug for which the application is submitted." *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

Accordingly, pursuant to 21 U.S.C. § 355(j)(5)(B)(iii), Merck initiated this suit against Actavis because Actavis' request to market the generic version of Noxafil® is prior to the expiration of the '151 patent.

In this action, a seven-day bench trial was held in July 2017. During trial, Actavis set forth the defense that filing of the ANDA application does not infringe the '151 patent because the asserted claims 11 and 12 of the '151 patent are invalid. In particular, Actavis asserted that—(i) claim 11 of the '151 patent is invalid because it is inherently anticipated by the European Patent Application EP 0 539 938 A1 ("EP '938"); and (ii) claim 12 is invalid because it is obvious to a person of ordinary skill in the art ("POSA") in view of the EP '938 reference.

In contrast, Merck argued that claims 11 and 12 of the '151 patent are valid because Actavis has not shown by a clear and convincing evidence that the asserted claims are rendered inherently anticipated or inherently obvious in view of the EP '938 reference. Further, Merck argued that the EP '938 reference is not a prior art reference under 35 U.S.C. §§ 102(a) and 103(a) because the inventive concepts recited in claims 11 and 12 of the '151 patent were invented on April 14, 1993, and diligently reduced to practice prior to or soon thereafter. As such, antedating the EP '938 reference, published on May 5, 1993.

Actavis arguably asserted that claim 12 is invalid because it is inherently anticipated by the EP '938 reference; however, the parties later stipulated that claim 12 is not inherently anticipated by the EP '938 reference. (*See* D.I. 199).

After careful review and consideration of the evidence presented at the bench trial, the Court finds that Merck has provided that the subject matter recited in claims 11 and 12 of the '151

patent was conceived on April 14, 1993, which was diligently reduced to practice thereafter. Thereby, rendering the EP '938 reference not a prior art reference to the '151 patent. As such, the Court finds that claim 11 of the '151 patent is not invalid under 35 U.S.C. § 102(a); and claim 12 of the '151 patent is not invalid under 35 U.S.C. § 103(a).

A. GOVERNING LAW

As we know the Leahy-Smith America Invents Act ("AIA") substantially changed the patent law on September 16, 2011. One such change amended the prior law from a 'first to invent' to 'first to file' system except in certain cases. The AIA further provided that the amendments set forth in the AIA would not take effect until eighteen (18) months after enactment (March 16, 2013). This matter arises prior to the effective date. As such, the pre-existing law applies. (*See* Manual of Patent Examining Procedure ("MPEP"), Section 2159.01); *also see* AIA 125 Stat. at *293 (Sec. 3(n)(1)).

B. PROCEDURAL BACKGROUND

The patent application of the '151 patent was filed on June 2, 1995, which later issued on August 26, 1997, to Schering Corporation ("Schering"). On August 30, 2012, Schering assigned its rights in the '151 patent to Merck.[1] The '151 patent was listed in the FDA's Orange Book in three different New Drug Applications ("NDA"), which are directed to an intravenous infusion solution (300MG/16.7ML (18MG/ML)); oral suspension (40MG/ML); and oral tablet with delayed release (100MG). The NDA, N205053, for the oral tablet with delayed release (100MG), is the one that Actavis seeks approval from the FDA to market and sell a generic version in the United States. (*See* Complaint ("Compl.") at ¶ 19; D.I. 1).On November 25, 2013, the FDA

[1] *See* Image File Wrapper ("IFW") of the '151 patent. Reel/Frame: 028884/0151; Recorded: 8/30/2012; *available at* https://portal.uspto.gov/pair/PublicPair (last visited, July 25, 2017).

approved Merck's NDA N205053, directed to oral tablet with delayed release (100MG), for use in "prophylaxis of invasive aspergillus and candida infections."[2]

In its ANDA filing with the FDA, Actavis included a written certification (¶ IV Certification) alleging that the claims of the '151 patent are invalid or otherwise will not be infringed by Actavis' ANDA product. (*See id.* at ¶ 20; *see also* 21 U.S.C. § 355(j)(2)(A)(vii)(IV)).

Consequently, on August 6, 2015, Merck initiated this suit against Actavis; alleging that Actavis' request to market the generic version of Noxafil® is prior to the expiration of the '151 patent. As such, infringing Merck's intellectual property rights granted under the '151 patent. (*See id. at* ¶¶ 26-30; *see also* 35 U.S.C. § 271(e)(2)).

Merck asserted claims 11 and 12 of the '151 patent against Actavis in this suit. (*See* First Amended Invalidity Contentions at 5; D.I. 67). Independent claim 11 being directed to the compound posaconazole, and dependent claim 12 being directed to a pharmaceutical composition comprising the posaconazole of claim 11 and a pharmaceutically acceptable carrier. Claim 12 depends from claim 11. (*Id.* at 6). In its invalidity contentions, Actavis asserted, *inter alia*, that claims 11 and 12 of the '151 patent are invalid because—(i) claim 11 is inherently anticipated by the EP '938 reference (*see id.* at 21); (ii) claim 12 is inherently anticipated by the EP '938 reference (*see id.* at 23); (iii) claim 11 is obvious in view of multiple grounds (*see id.* at 23-34); and (iv) claim 12 is obvious in view of the EP '938 reference (*see id.* 35-36).

At trial, Actavis bearing the burden to invalidate the asserted claims of the '151 patent, presented mainly expert evidence to show that the asserted claims 11 and 12 of the '151 patent as

[2] *See* U.S. Food & Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Patent and Exclusivity for: N205053. Product 001, Posaconazole (Noxafil) Tablet, Delayed Release 100MG, (Patent Use Code: U-1454), *available at* https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=205053&Appl_type=N (last visited, July 25, 2017).

being invalid as noted above. The experts were—Dr. Paul Ortiz De Montellano; Dr. Stanley Roberts; Dr. Wei Lu; Dr. Gary Glick; Dr. Edwin P. Alyea; and portions of videotaped depositions of Dr. Viyoor M. Girijavallabhan ("Dr. Giri"), Dr. Frank Bennett, and Mr. Frank Lovey.

On the other hand, Merck defended the '151 patent by arguing that the asserted claims 11 and 12 are not inherently anticipated or rendered obvious in view of the EP '938 reference. Further, Merck argued that the EP '938 reference does not qualify as a prior art reference because the posaconazole compound recited in claim 11 and the pharmaceutical composition recited in claim 12 were conceived before the publication date of the EP '938 reference (May 5, 1993), and diligently reduced to practice soon thereafter. In order to advance these positions, Merck relied on the following witnesses and experts—Dr. Birendra N. Pramanik; Dr. Anil Saksena; Dr. Roland Dolle; Dr. Fredrick P. Guengerich; Dr. Mahmoud Ghannoum; Dr. Kieren Marr; Dr. Giri; Dr. Raymond Lovey; and Dr. Frank Bennett.

At the end of the trial, the parties submitted proposed findings of fact and conclusions of law, followed by reply papers. (*See* Pl.'s Findings of Fact ("FoF"), D.I. 200; Def.'s FoF, D.I. 201; Def.'s Conclusions of Law ("CoL"), D.I. 204; Pl.'s CoL, D.I. 205; Def.'s Reply, D.I. 208; Pl.'s Reply, D.I. 209).

The issues litigated before the Court were whether—(1) Merck can antedate the EP '938 reference by showing that the claimed subject matter of claims 11 and 12 were conceived before the publication date of the EP '938 reference, and diligently reduced to practice soon thereafter; and (2) if the EP '938 reference is a prior art reference to the '151 patent, is claim 11 inherently anticipated by the EP '938 reference under the pre-law; and (3) if the EP '938 reference is prior art, is claim 12 rendered obvious under the pre-law. (*See* Def.'s FoF at ¶ 3; *see also* Pl.'s FoF at ¶ 16).

C. CONVENTIONAL TECHNOLOGY & DRUG DEVELOPMENT

In or around 1993 (the time of the inventive concepts disclosed in the ’151 patent) there was a need for broad-spectrum antifungal agents with increased solubility and favorable activity profile for treating systemic fungal infections. In particular, systemic fungal infections such as, Aspergillus, Candida, Cryptococcus and opportunistic infections, needed to be treated. (*See* the ’151 patent, col. 2, ll. 27-32).

During the early 1990s, when the HIV/AIDS disease was very high, and there were many immune-suppressed patients, medical professionals in this field were aware of the need to cure or treat fungal infections more effectively. (*See* Plaintiff’s Expert, Dr. Kieren Marr’s testimony Transcript (“Trans.”) at 1185:19-24, 1195:21—1196:10 (Marr), dated July 19, 2017). Dr. Marr testified that there are two types of fungal infections—local and systemic functions. Distinguishing between them, she stated that a local fungal infection, such as athlete’s foot is limited to an external part of the body; but systematic fungal infections involve fungal invasion of more than one organ system, such as the blood, lungs, or brain, which are caused by yeasts and molds such as Aspergillus, Candida, Zygomycetes, Cryptococus, and Coccidioides. Systemic fungal infections being prevalent in persons who have compromised immune systems. (*See* Trans. at 1191:22—1194:10 (Marr); *see also* Pl.’s FoF at ¶¶ 70-73).

Dr. Marr, “an expert in infection diseases, particularly the pathogenesis, diagnosis and prevention and treatment of fungal infections” (*see* Trans. at 1188:3-6), testified that one of the drugs available to physicians in the year 1993 to treat people with fungal infections was Amphotericin B, which was administered intravenously. The side effect of this drug was that it caused severe kidney destruction; resulting in fevers and chills. (*See* Trans. at 1194:16-25 (Marr); *see also* Pl’s FoF at ¶¶ 79, 81).

Next, Dr. Marr noted that the other conventional drugs included—Flucytosine, Ketoconazole, Fluconazole, and Itraconazole. (*See* PX 1057). Dr. Marr testified that in 1993, the only antifungal drugs available for physicians to prescribe for systemic fungal infections were the aforementioned drugs. (*See* Trans. at 1202:3-7). All of these conventional drugs have a broader spectrum than their predecessor, but they have significant side effects. For example, Flucytosine had limited usage because fungal infections became rapidly resistant to this drug (*see* Trans. at 1196:20-23); Ketoconazole, approved by the FDA in 1981, created toxicities in the liver when it interacted with the P450 enzyme (*see* Trans. at 1197:1-6; *see also* Pl.'s FoF at ¶¶ 83, 84); Fluconazole, which was considered very safe, had activity against Candida species, but had no activity against molds (i.e., Zygomycetes) (*see* Trans. at 1198:19—1199:3, 1200:9-10); and lastly, Itraconazole, approved by the FDA in 1992, was effective against molds (Aspergillus); but Itraconazole was not very effective in treating people with suppressed immune systems, and was not safe for patients with heart defects. (*See* Trans. at 1200:11-25; *see also* Pl.'s FoF at ¶ 86).

Moreover, Dr. Marr testified that in the late 1980s and the early '90s there were no FDA approved drugs available to prevent or treat patients that were susceptible to fungal infections, there was only conventional amphotericin B. (*See* Trans. 1203:24—1204:1). As such, there was a pressing need for a broad spectrum drug that could be administered for preventive use for diabetic patients, AIDS patients and transplant patients. (*See* Pl.'s FoF at ¶ 88).

Similarly, Dr. Dolle, Merck's expert in drug discovery and medicinal chemistry (*see* Trans. at 538:18-21), concurred with Dr. Marr about the ongoing need for antifungal drugs. In 1940s, Benzimidazole, a forerunner of azole class, was introduced in the market, which had weak activity against fungi. (*See* PX 1017). Then in the 1960s, Miconazole, a topical agent to treat things like fungus and ringworm, was approved by the FDA around 1960s. Thereafter, in 1977, Ketoconazole

was approved, which was the first oral active agent. (*See* Trans. at 727:12-25 (Dolle)). Ketoconazole, the first orally active compound, lead further interest by the scientific community into following up on azoles in treating antifungal infections. (*Id.* at 728:3-8 (Dolle)).

Dr. Dolle further noted that developing a new antifungal drug is a long drawn out process. (*See* PX 1002). He explained that the pre-clinical phase a lead compound is identified, optimized, and then tested in animals. Whereas, under the clinical phase, the lead compound is tested in humans; and the assessment of the lead compound's efficacy and safety in humans is determined, before being approved by the FDA. (*See* Trans. at 541:25—542:1-7 (Dolle)).

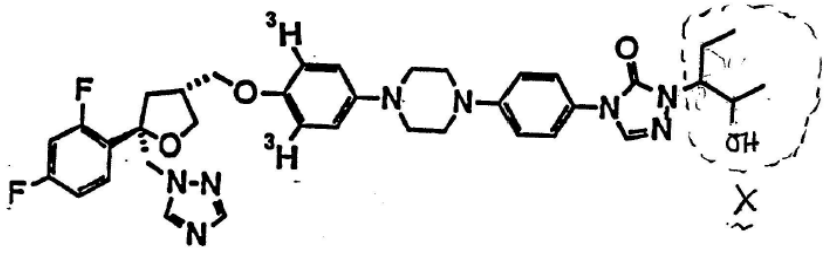
In summary, Dr. Dolle noted that it is an industry average that around 10,000 compounds that are synthesized or evaluated for their biological activity under the pre-clinical phase. Only 0.1% percent of those compounds enter the clinical phase, out of which only 10% have a chance of getting FDA approval. (*See* Trans. at 542:8-23 (Dolle)). Consequently, the entire process may exceed ten (10) years from possessing a lead compound through the clinical phase and obtaining FDA approval. (*See* Trans. 542:21—543:3 (Dolle)).

D. DEVELOPMENT OF POSACONAZOLE

In early 1993, Schering performed studies on Compound IIc (i.e., SCH-51048). The research and studies indicated that when Compound IIc was administered to mice, there was a compound within mice's blood that had better antifungal activity than its parent compound (Compound IIc). This suggested to the scientists at Schering, in particular Dr. Saksena, that some metabolite of Compound IIc was more active than the parent compound itself. (*See* Pl.'s FoF at ¶ 108; *citing* Trans. at 472:4-19; 1353:16-19; JX 44.0027; JX 44.0036). This active metabolite was called "Metabolite A."

Although Dr. Saksena learned about the existence of this active metabolite, Metabolite A, he did not have any idea or mental conception of the structure of this active metabolite. (*See* Pl.'s FoF at ¶ 114). As such, Dr. Saksena and his colleagues attempted to learn more about the structure of this metabolite by undertaking further research. (*Id.* at ¶ 117). On April 13 and 14, 1993, Dr. Larry Heimark, a mass spectrometrist, performed serum samples of the antifungally active CF-1 mouse metabolite of Compound IIc. (*Id.* at ¶ 118; *citing* JX 7.0003-05). Dr. Birendra Pramanik, a senior mass spectrometrist and Dr. Heimark's supervisor, analyzed the mass spectra provided by Dr. Heimark and wrote down the results of his analysis in his lab notebook. (*Id.* at ¶¶ 119-120). These results are shown below—

SCH 51048 Metabolite



LC/MS, LC/MS/MS data of metabolite sample indicated that the compound is a secondary alcohol; oxidation is occured at the side chain (X). This information led to the synthesis of primary and secondary side chain alcohols. The electrospray MS/MS spectra suggested the structure to be a secondary alcohol as shown above (*tentative). More works ~~vas~~ continuing.

(*See* JX 7.0001). Dr. Pramanik's handwritten remarks (above) are difficult to read but in substance the notes state that this structure, as labeled as "SCH 51048 Metabolite," is—(i) data of the

metabolite sample indicated that the compound is a secondary alcohol; (ii) oxidation occurred at the side chain (X) (annotated in the figure); and (iii) additional work is in progress.

On the same day, April 14, 1993, Dr. Pramanik discussed his findings and mass spectra with Drs. Saksena and Giri. Based on the evidence before them, Drs. Pramanik, Saksena and Giri perceived that Metabolite A could have any of seven possible structures. These seven possibilities included—two primary alcohols, four secondary alcohols, and one tertiary alcohol. (*See* Pl.'s FoF at ¶¶ 121-124). "Primary" and "secondary" refer to the specific carbon to which the OH group is attached. (*See* Def.'s Br. at 4). The tertiary alcohol was quickly ruled out during this meeting, and on April 14, 1993, they decided to synthesize and test each of the six alcohols to determine which one of the six alcohols had antifungal activity. (*See* Pl.'s FoF at ¶ 127; *citing* Trans. at 476:13-20 (Saksena); 1145:21—1146:2 (Giri); and 1337:25—1338:2 (Glick)).

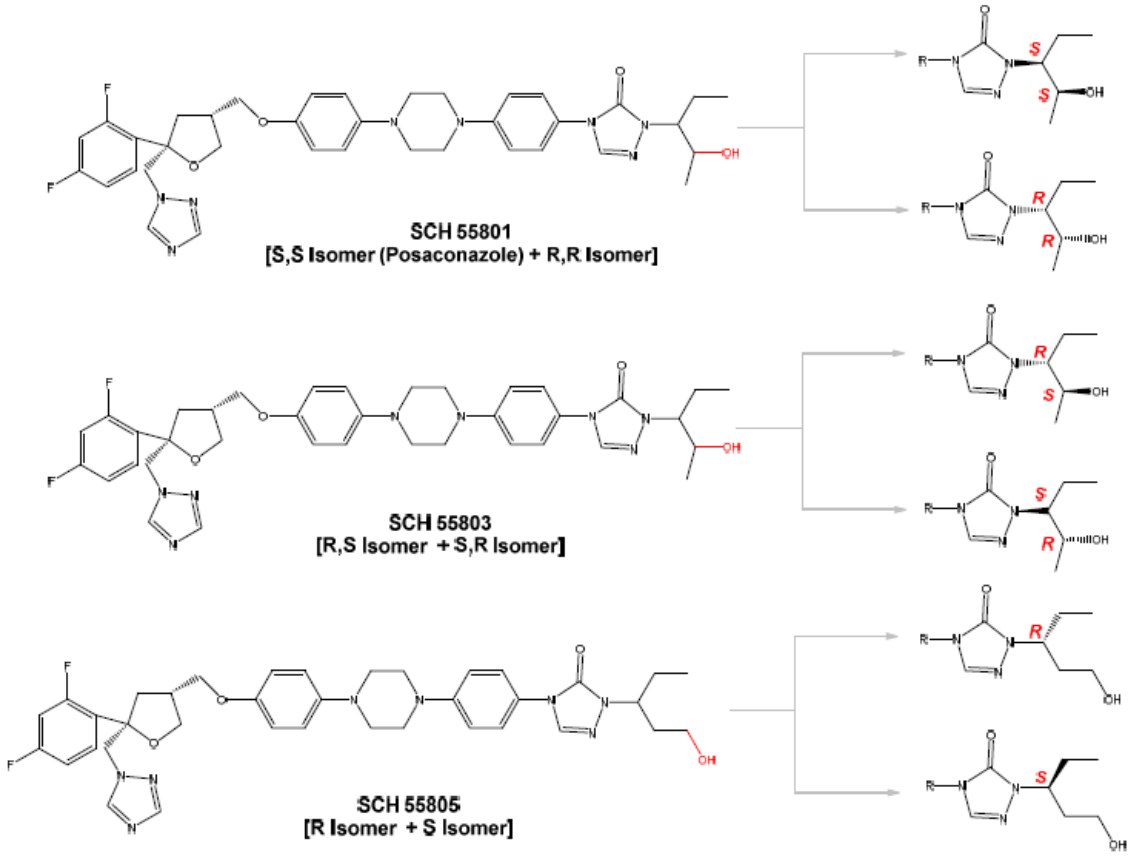
The six alcohols were synthesized as three pairs of racemates (i.e., as three mixtures, each containing a pair of two distinct stereoisomers) for purposes of synthetic convenience, as the three racemates could be more quickly prepared; resulting in an early evaluation of the biological activity of the compounds. (*See* Pl.'s FoF at ¶¶ 128-129).

Both posaconazole and SCH-51048 are each single "stereoisomers." In a general sense, this means that each compound has a corresponding pair compound that has the same atoms, attached in the same way, but with a non-superimposable mirror-image configuration in three-dimensional space, similar to left and right hands. (*See* Trans. at 60:11-61:17; 62:23-63:23) (Ortiz De Montellano). These mirror-image compounds are denoted as "(*R*)" and "(*S*)" forms of the compound. (*See* Trans. at 62:20-22; 63:24-64:3) (Ortiz De Montellano). The different stereoisomers of a molecule often have different biological activity and/or toxicity. One well-known example of this phenomenon is the drug thalidomide. The (*R*) form of thalidomide is

effective against morning sickness, while the (*S*) form causes birth defects. (*See* Trans. at 64:23-65:11) (Ortiz De Montellano). *See* Def.'s FoF at ¶¶ 11-12.

The purpose of synthesizing the six alcohols was to test their activity against fungal agents, both *in vivo* and *in vitro*, and ultimately determine if any of these compounds could be developed into marketable drugs. (*Id.* at ¶ 132). To test each of the six alcohols *in vivo*, each of them would have to be formulated as a pharmaceutical composition containing a potentially antifungally effective amount of posaconazole suitable for administration to laboratory animals suffering from fungal infections. (*Id.* at ¶ 133).

The synthesis of the six alcohols, which were determined during the April 14, 1993, meeting between Dr. Giri, Dr. Saksena and Dr. Pramanik, was assigned to Mr. Raymond Lovey. (Def.'s FoF at ¶ 25). Mr. Lovey was tasked to synthesize three racemic mixture, or racemate, (mixtures of two stereoisomers), SCH-55801, SCH-55803, and SCH55805. (*Id.* at ¶ 26; Pl.'s FoF at ¶ 148). The three pairs of the racemic mixtures are shown below—



(*See* Pl.'s FoF at ¶ 180). SCH-55801 and SCH-55803 corresponded to the four secondary alcohols of SCH-51048, and SCH-55805 corresponded to the two primary alcohols of SCH-51048. (*Id.* at ¶ 181).

During the April 14, 1993 meeting, Drs. Giri and Saksena provided Mr. Lovey with an outline of the synthetic steps to make the racemates. (*See* Pl.'s FoF at ¶ 150). Mr. Lovey's five-step synthesis of SCH-55801 started on April 26, 1993 and was completed by May 26, 1993. (*Id.* at ¶ 154). The five-steps included—(i) dihydroxylation of 2-pentene (step 1); (ii) protection of 2,3-pentanediol (step 2); (iii) sulfonation of SEM protected 2,3 pentanediol (step 3); (iv) coupling of triazole core (step 4); and (v) deprotection to remove SEM protecting group, yielding posaconazole and its enantiomer (step 5). (*See* PX 1010; Pl.'s FoF at ¶ 182-183).

On May 26, 1993, Mr. Lovey made SCH 55801, posaconazole, as a one-to-one mixture with the R,R isomer. (*See* Pl.'s FoF at ¶¶ 184-185). A mass spectra analysis done on June 14, 1993 indicated SCH-55801 had the distinctive fragmentation pattern of the secondary alcohol analogs of SCH-51048. (*Id.* at ¶ 187). The three racemic mixtures Mr. Lovey synthesized were tested in *in vitro* experiments, which showed that all had activity and that they were more active than SCH-51048. (*Id.* at ¶ 190).

After the three racemic mixtures—SCH-55801, SCH-55803 and SCH-55805—were tested for *in vitro* antifungal activity, Drs. Giri and Saksena directed their team to make the six alcohols in pure form. (*Id.* at ¶ 197). Dr. Bennett, one of the Schering scientists tasked with making the pure form, began his work on June 30, 1993, and concluded the synthesis of pure posaconazole on August 20, 1993. (*Id.* at ¶ 200). Dr. Bennett began with synthetic routes to the azole core and the piperazine linker 'in hand,' and attached the side chain necessary to make posaconazole as a pure compound. (*Id.* at ¶¶ 159-160). As such, Dr. Bennett was the first person to make SCH-56592, which was later known as posaconazole, not in a mixture with its RR enantimoer. (*Id.* at ¶ 199). The *in vivo* testing showed that SCH 56592 (posaconazole) had the best oral activity, the best pharmacokinetics, and the best efficacy of the six individual stereoisomers. (*Id.* at ¶ 203).

By October 18, 1993, a protocol for testing all six secondary and primary alcohol analogs of SCH-51048, including posaconazole, in mice infected with *Candida albicans* was in place; and testing of the six alcohols as pharmaceuticals began. (*Id.* at ¶ 209). Between October 18, 1993 and December 21, 1993, posaconazole was tested *in vivo*, the results were analyzed, and 171,083 patent application ("'083 patent application") was filed. (*Id.* at ¶ 211).

E. THE '151 PATENT

A. EARLIEST PRIORITY DATE

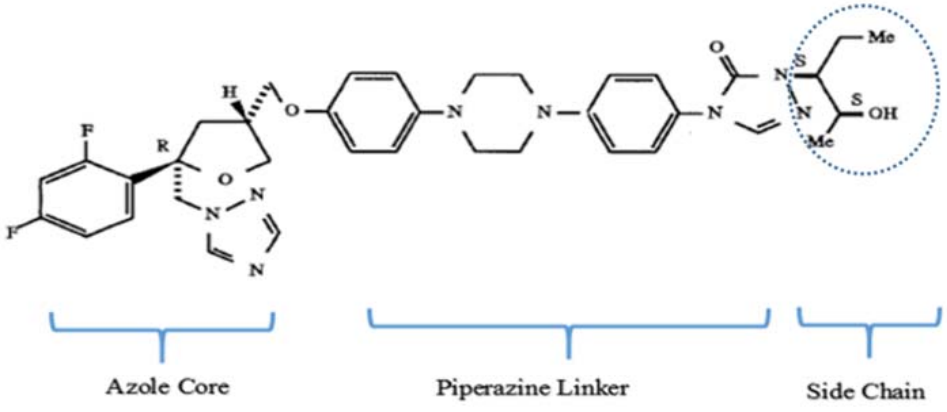
The parties agree that the earliest priority date of the '151 patent is December 21, 1993. (*See* First Amended Invalidity Contentions at 6). The '151 patent is a continuation-in-part ("CIP")[3] application of a PCT application, and the PCT application is a CIP application of the '083 patent application ("'083 patent application").

B. DISCLOSURE OF THE '151 PATENT

The '151 patent is generally directed to the synthesis and clinical use of antifungal compound posaconazole, which is used for treating and/or preventing fungal infections. (*See* Abstract of the '151 patent). Posaconazole is an azole antifungal, which means it is a particular class of chemical compounds that are known to have antifungal activity. (*See* Trans. at 7:8-14). The '151 patent discloses antifungal compounds of formula I and pharmaceutical compositions, which are expected to exhibit anti-allergic, anti-inflammatory and immunomodulating activities. The pharmaceutical composition contains a fungicidally effective amount of other antifungal compounds. (*Id.* at col. 56, ll. 40-67).

The chemical structure of posaconazole, which shows the arrangement of the atoms within the molecules and which atoms are bonded together, and whether single, double or triple bonds are formed between, is illustrated in claim 11—

[3] *See* MPEP 201.08 ("A continuation-in-part application is an application filed during the lifetime of an earlier nonprovisional application, repeating some substantial portion or all of the earlier nonprovisional application and *adding* matter not disclosed in the earlier nonprovisional application.").



Posaconazole

(*see* the ’151 patent, col. 78, ll. 1-20; *see also* Def.’s Br. at 2; D.I. 162; *see also* Def.’s FoF at ¶ 9 (“there are three parts to the posaconazole structure, the azole core, the piperazine linker and the side chain.”); *see also* Pl.’s FoF at ¶ 134). Dr. Dolle, Merck’s expert, testified that the chemical structure of the posaconazole compound is a three-dimensional structure, wherein the dashed lines and the bold solid lines, as illustrated above, represent groups behind the plane and coming out of the plane, respectively. (*See* Trans. 563:24—564:3 (Dolle)).

The ’151 patent further discloses that pharmaceutical compositions are formulated by combining the compound of formula I or an equivalent amount of a pharmaceutically acceptable salt of compound I *with* a suitable, inert, pharmaceutically acceptable carrier or diluent. Examples of suitable pharmaceutical compositions include solid or liquid compositions for oral administration such as tablets, capsules, pills, powders, granules, solutions, suppositories, troches, lozenges, suspensions or emulsions. (*Id.* at col. 57, ll. 40-50).

Further, the ’151 patent discloses that a solid carrier can be one or more substances which may act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders or tablet disintegrating agents, or as an encapsulating material. The carrier can also be a finely divided solid

which is in admixture with the finely divided active compound. In a tablet form, for example, the active compound is mixed with the carrier that has the necessary binding properties. The carrier is added in suitable proportions such that the tablet is compacted in the desired shape and size. (*Id.* at col. 57, ll. 45-55).

During prosecution of the patent application of the ’151 patent, the examiner rejected the claimed subject matter. The Applicant amended the then pending claims to include claim term “in vivo” to differentiate over the cited art. (*See* Image File Wrapper of the ’151 patent, Applicant’s Arguments/Remarks Made in an Amendment, filed May 24, 1996). This amendment was made in response to patent examiner’s rejection mailed on November 22, 1995. Additionally, arguments against the obviousness rejection under 35 U.S.C. § 103 were also made. (*Id.*)

After mailing a final rejection on August 21, 1996, the examiner conducted a personal interview with the Applicant’s representative. During the personal interview, the enablement rejection under pre-AIA 35 U.S.C. § 112, first paragraph, was discussed, and the Applicants agreed to provide an affidavit demonstrating that enablement exists for use of “in vivo” esters. (*See* Examiner Interview Summary Record mailed on December 19, 1996).

Thereafter, the Applicant filed a response to the outstanding Office action with a declaration from Dr. Ashit K. Ganguly, a co-inventor of the ’151 patent. In the response, the Applicant essentially argued that based on the specification a POSA would be able to readily determine which of the ester compounds would be soluble or suspendible in a pharmaceutically acceptable aqueous media. (*See* Applicant’s Arguments/Remarks filed on January 29, 1997; *citing* Declaration of Dr. Ganguly at ¶ 17).

Further, Applicants noted that they are “amending claim 17 of this application to cover a preferred embodiment, and to recite that such esters of the compounds of the claimed invention

have a solubility in a pharmaceutically acceptable media of at least about 1 to about 50 mg/ml." (*Id.* at 6). Thereafter, on February 7, 1997, a notice of allowance was mailed by the patent examiner, which was later followed by a corrected notice of allowance on February 27, 1997. No reasons for allowance in-particular were provided by the patent examiner when issuing the notice of allowance.

F. THE EP '938 REFERENCE & THE NOMEIR 2008 REFERENCE

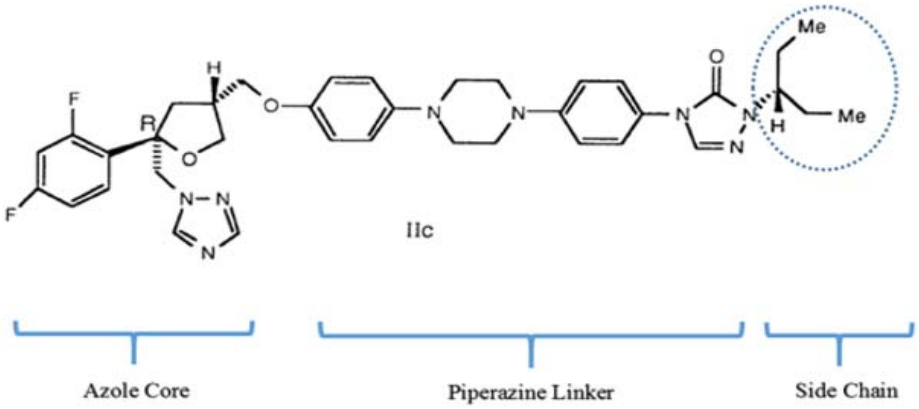
The EP '938 reference, assigned to Schering, is the prior art primarily relied upon by Actavis to invalidate asserted claims 11 and 12 of the '151 patent as being inherently anticipated and obvious. Since the EP '938 reference became publicly available on May 5, 1993, and the patent application date of the '151 patent being December 21, 1993, Actavis argues that the EP '938 reference is a prior art reference. (*See* Trans. at 6:8—7:5; 43:21-23).[4] Notably, the inventors of the EP '938 reference are Dr. Saksena, Dr. Ganguly and Mr. Lovey.

The EP '938 reference identifies that there is a need for broad spectrum antifungal agents to treat systematic fungal infections, especially Aspergillus and Candida infections. (*See* the EP '938 reference at page 3, ll. 28-29). The EP '938 reference describes three compounds, designated as Compounds IIa, IIb, and IIc, wherein Compound IIc being the "more preferred" compound. (*Id.* at page 3, ll. 54). Compound IIa referred to SCH-50001; Compound IIb referred to SCH-50002; and Compound IIc referred to SCH-51048, respectively. (*See* Pl.'s FoF at ¶ 104). The EP '938 reference discloses that itraconazole, fluconazole, and saperconazole were tested for *in vivo* oral

[4] Actavis' Counsel: ("[C]laim 11 is anticipated by […] [EP-938 because] EP-938 describes administering a compound called compound IIc [SCH-51048] to mice. […] Compound IIc, when it's administered to [a] mice, it necessarily metabolizes to the claimed compound posaconazole. And under the Federal Circuit's precedent, particularly the *Schering* decision, that makes claim 11 anticipated or inherently anticipated by EP-938. […] With respect to claim 12, Actavis is going to prove by clear and convincing evidence that a person of ordinary skill in the art […] would have combined [compound IIc] with a pharmaceutically acceptable carrier, and would have a reasonable expectation of success.").

antifungal activity in a Candida systemic model using CF-1 male mice, average weight being 20 grams. (*See* the EP ’938 reference at page 33, ll. 6-14).

Dr. Ortiz de Montellano, Actavis’ expert in the field of drug metabolism and the identification of drug metabolites (*see* Trans. at 58:6-11), relied upon page 15, column 37-50, of the EP ’938 reference, to testify that this reference discloses the administration of Compound IIc or SCH-51048 into CF-1 male mice who are infected with Candida allergens (a fungal strain). (*See* Trans. at 90:2-8). Compound IIc, which includes— the azole core, the piperazine linker, and the side chain—similar to posaconazole, has the following chemical structure—



Compound IIc (SCH-51048)

(*see* the EP ’938 reference at page 15, ll. 35-50; *see also* Def.’s FoF at ¶ 10 (“[Compound IIc] has the same structure as posaconazole except for the omission of an OH, or hydroxyl, group on the side chain.” (*citing* Trans. at 59:3—60:3)); *see also* Pl.’s FoF at ¶ 135). Dr. Ortiz de Montellano testified that in his opinion when Compound IIc is administered to a 20 gram CF-1 male mice, it is metabolized by the mice’s liver into posaconazole. Dr. Ortiz de Montellano based this opinion both on literature disclosures regarding the *in vivo* metabolism of Compound IIc and on *in vitro*

experiments conducted in his laboratory. (*See* Trans. at 98:7-15, 98:25—99:1-2; *see also* Opening Expert Report of Dr. Ortiz De Montellano at ¶ 4; Cross Exhibit ("CX") 0742.0001).

Additionally, relying on a publication from 2008, commonly referred to as the Nomeir 2008 publication (JX 0033)[5], Dr. Ortiz de Montellano testified that the Nomeir 2008 publication describes how pre-clinical metabolism studies with SCH-51048 or Compound IIc led to the development of currently marketed drug posaconazole (SCH-56592). In particular, Dr. Ortiz de Montellano notes that the Nomeir 2008 publication discloses that when SCH-51048 was dosed to various mammal species, the presence of an active metabolite[6] ("Metabolite A") was discovered. (*See* Expert Report of Dr. Ortiz De Montellano at ¶ 15 (*citing* Nomeir 2008 at 512-517); CX 0742-0010-0011; *see also* Trans. at 91:18-24 (Dr. Ortiz De Montellano):

> "Note that they did not actually go looking for an active metabolite, they actually just administered looking at the kinetics to see how long the drug would be active in the mice, and what they basically found is that in fact activity lasted much longer than the compound SCH-51048 which implicated an active metabolite. And this eventually led to the discovery of posaconazole."

The Nomeir 2008 publication discusses that when Compound IIc was administered to different species—mice, rabbits, dogs and cynomolgus monkeys—the majority of radioactivity determined in serum was due to metabolites rather than the parent compound (i.e., Compound IIc). Presence of two metabolite peaks (A and B) were identified. (*See* JX 33.0006-0007). The electrospray mass spectral data established that the molecular weight of metabolite A was 701 Daltons, which was 16 mass units greater than the parent Compound IIc (m/z 685). (*Id.*). Based

[5] *See* Nomeir, Amin A., *et al.*, "Posaconazole (Noxafil, SCH 56592), a new azole antifungal drug, was a discovery based on the isolation and mass spectral characterization of a circulating metabolite of an earlier lead (SCH 51048)." JOURNAL OF MASS SPECTROMETRY, 43:509-517 (2008).

[6] *See* Trans. at 237:17-21 ("[Actavis' Counsel] Q: Dr. [Wei] Lu, what is a metabolite? A: Metabolite is as Dr. Ortiz mentioned last Thursday, some apparent compounds or drugs can be structured can change in vivo or in vitro situation, to others structures, that is identified as metabolite.").

on the testing conducted, and by a process of deduction, the active metabolite A was "pinpointed, isolated, purified, and by the use of the powerful LCMS/MS [liquid chromatography-tandem mass spectrometry] technology was very quickly characterized as a secondary alcohol. [As such] […] posaconazole emerged as the compound with the best overall profile." (Id. at 0033.0009; see also Trans. at 92:20-25).

Dr. Wei Lu, Actavis' expert witness, testified that based on his study of the Compound IIc disclosed in the EP '938 reference, and reliance on the disclosure of the Nomeir 2008 publication, he was able to conclude that posaconazole is necessarily formed in a mouse's liver starting from the Compound IIc. That is, the Nomeir 2008 publication describes the discovery of posaconazole based on the metabolism of the Compound IIc. (*See* Trans. at 240:12-16; 241:3-9[7]; 247:15-22).

In his laboratory, Dr. Lu employed liver microsomes prepared from 20 gram CF-1 male mice, in order to metabolize the Compound IIc. Through experimentation, he collected data that recorded retention time, mass, and fragmentation pattern of an incubation mixture. Dr. Lu analyzed the incubation mixture to confirm that posaconazole is present. (*See* Trans. at 245:14-19; *see also* Def.'s FoF at ¶ 4).

Dr. Gary Glick, also Actavis' witness, testified that the EP '938 reference discloses when Compound IIc, which when administered to CF-1 male mice it is necessarily metabolized into posaconazole. Dr. Glick based this opinion on a series of documents made available by Schering and testing performed by Dr. Lu and synthesis of Compound IIc performed by Dr. Stanley Roberts. (*See* Trans. at 316:14-24). Dr. Glick noted that goal of Dr. Lu's experiments was to indicate that metabolite A or posaconazole was formed upon treating animals with Compound IIc, and the only

[7] ("Q: Why did you obtain only these four standards? A: Because they cited in the Nomeir paper, year 2008, that these four structures of interest is the secondary alcohol generated in their experiment.").

thing left to do was to determine the stereochemistry[8] of the metabolite. (*See* Trans. at 330:10-13 ("Q: Do you agree with Dr. Lu's conclusion that posaconazole is formed from the incubation of SCH-51048 [Compound IIc] in CF-1 mouse liver microsomes? A: Based on the data that I have reviewed, yes.").

Further, in relying upon the Nomeir 2008 publication, Dr. Glick testified that this reference discloses that Schering was in the process of testing Compound IIc in animals as it was a very promising compound, and during the process of routine testing, an active metabolite was discovered. The structure of this active metabolite was deduced using standard experiments in organic chemistry such as mass spectrometry and LCMS/MS. (*See* Trans. at 317:23—318:9).

In referring to the Nomeir 2008 publication, in particular the mouse model shown in figure 2 of this reference, Dr. Glick testified that Compound IIc was injected into the mice, and after a period of time blood was obtained from the injected mice, and the blood samples were analyzed, wherein metabolite A was found. The structure of which was deduced using the LCMS/MS technology. (*See* Trans. at 320:12-23). Further, in reference to figure 8 of the Nomeir 2008 publication, Dr. Glick testified that as to the structure of metabolite A, the scientists at Schering noted that there were three possible places that the hydroxyl (OH) group could be placed on the side chain. And, based on the potential chemical stability of the resulting product that the tertiary

[8] *See* Trans. at 326:15-24 ("[Actavis' Counsel] Q: And when you say stereochemistry what do you mean? A: So where it was pointing in space dictates the chemical nature of the molecule, and molecular atoms that point in different orientations in space are defined as different -- they're call stereoisomers. […]. Q: How many stereoisomers are there for metabolite A? A: There are four possible stereoisomers, one of which is posaconazole.").

Also see Trans. at 895:13—896:19, in understanding the concept of "stereoisomer," Merck's Counsel, Mr. Chesler, put forth a shoe analogy on re-direct examination of Dr. Dolle. ("Q: What if any relevance does [shoe] analogy have to the stereochemistry that relates to what Mr. Lovey made in May of 1993? A: […] Mr. Lovey made the one-to-one mixture of posaconazole in the mixture, it's basically the right hand – it's a right hand and a left hand, he made a mixture of both of those. So […] if you go back to the shoe analogy […] this is a case where he synthesized the pair and clearly posaconazole is there.").

carbon was not going to be a site of metabolism. Instead, primary or secondary carbons were the site of metabolism. (*See* Trans. at 323:2-11).

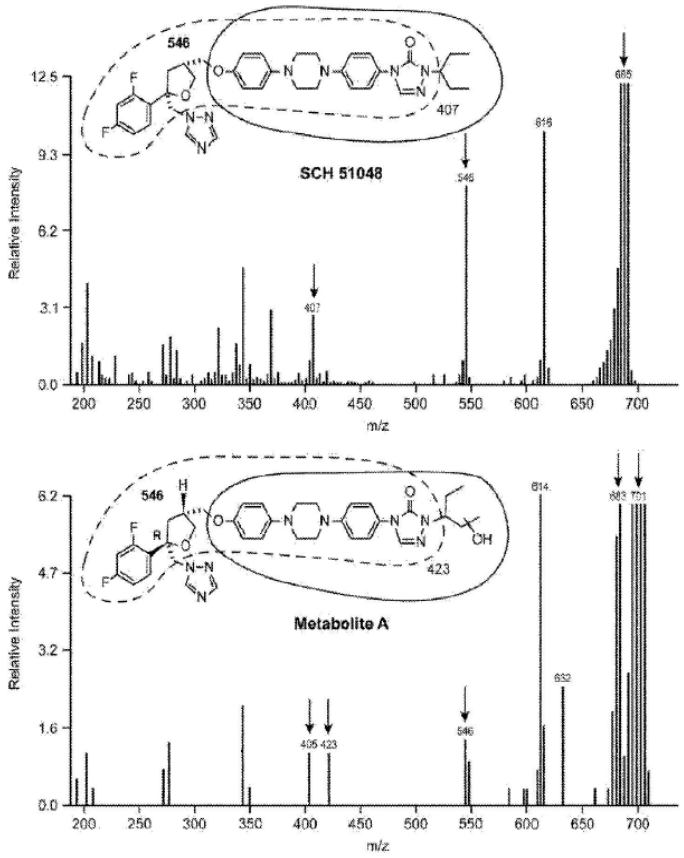


Figure 4. Mass spectra of SCH 51 048 and the active metabolite (metabolite A) isolated from mouse serum. Metabolite A ($m/z = 701$), with 16 mass units greater than SCH 51 048 ($m/z = 685$), suggested the introduction of oxygen.

With respect to figure 4 of the Nomeir 2008 publication, Dr. Glick testified that the bottom graph illustrated in figure 4 shows mass spectral data of metabolite A. Figure 4 showing molecular weight (m/z) along a x-axis and intensity measure along a y-axis. The lines generated in the spectra from the data collected enable chemists to determine or propose the actual chemical structure. Dr. Glick noted that the bottom graph of figure 4 illustrates a proposed structure of metabolite A.

Unlike the chemical structure illustrated in the top portion of figure 4, which depicts the chemical structure of Compound IIc, the bottom portion of figure 4 illustrates the chemical structure of metabolite A with the hydroxyl group as part of the side chain. The hydroxyl group in

metabolite A is drawn in such a way with "sort of a line in the middle of what looks like a bond, because at this point the authors had not determined which atom it's attached to, so that's meant to mean indeterminate." (*See* Trans. at 321:1—322:13).

In conclusion, based on his review of the EP '938 reference and the Schering's internal documents, Dr. Glick concluded that it was clearly evident that posaconazole is necessarily and inevitably formed when Compound IIc is metabolized by the liver microsomes extracted from the CF-1 male mice. (*See* Trans. at 316:14-16).

STANDARD OF PROOF

By statute a patent is valid upon issuance. *See* 35 U.S.C. § 282(a). "Since we must presume a patent valid, the patent challenger bears the burden of proving the factual elements of invalidity by clear and convincing evidence ... The trial court has the responsibility to determine whether the challenger has met its burden by clear and convincing evidence by considering the totality of the evidence, including any rebuttal evidence presented by the patentee." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359-60 (Fed. Cir. 2007); *see also Microsoft Corp. v. i4i Ltd. P'ship, et al.*, 131 S.Ct. 2238, 2239 (2011).

Invalidity is an affirmative defense that "can preclude enforcement of a patent against otherwise infringing conduct." *Commil USA, LLC v. Cisco Systems, Inc.*, 135 S.Ct. 1920, 1929 (2015) (*citing* 6A Chisum on Patents § 19.01, p. 19-5 (2015)); *see also* 35 U.S.C. § 282(b)(2). The claims of a patent can be invalid for "fail[ing] to meet the conditions for patentability within the meaning of the patent law, Title 35 § 101 *et seq*., including, but not limited to, §§ 101, 102, 103 and/or 112." *Senju Pharmaceutical Co., Ltd. v. Apotex, Inc.*, 921 F.Supp.2d 297, 303-304 (D.Del. 2013).

35 U.S.C. § 102

Under 35 U.S.C. § 102, the anticipation inquiry, "invalidity [] requires that the four corners of a single[ ] prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000).

A single prior art reference may expressly anticipate a claim where the reference explicitly discloses each and every claim limitation. However, the prior art need not be *ipsissimis verbis* (i.e., use identical words as those recited in the claims) to be expressly anticipating. *Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984). A single prior art reference also may anticipate a claim where one of ordinary skill in the art would have understood each and every claim limitation to have been disclosed inherently in the reference. *Cont'l Can Co. USA Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991).

The Federal Circuit has explained that an inherent limitation is one that is necessarily present and not one that may be established by probabilities or possibilities. *Id.* That is, "the mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* The Federal Circuit also has observed that "inherency operates to anticipate entire inventions as well as single limitations within an invention." *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003).

The burden of proof to show anticipation rests on the party asserting invalidity and can be met only by clear and convincing evidence. *Microsoft Corp.*, 131 S.Ct. 2238. The Federal Circuit discussed the standards for inherent disclosure:

> "[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the

> single anticipating reference. However, a patent claim cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled. The standard for what constitutes proper enablement of a prior art reference for purposes of anticipation under section 102, however, differs from the enablement standard under section 112. It is well-settled that utility or efficacy need not be demonstrated for a reference to serve as anticipatory prior art under section 102."

Verizon Services Corp. v. Cox Fibernet Virginia, Inc., 602 F.3d 1325, 1337 (Fed. Cir. 2010) (internal quotation marks and citations omitted).

35 U.S.C. § 103

Under 35 U.S.C. § 103(a), the obviousness inquiry, "a patent may not be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art." Obviousness is a question of law that is predicated on several factual inquiries. *Richardson—Vicks v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997).

Specifically, the trier of fact is directed to assess four considerations: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness, such as commercial success, long felt but unsolved need, failure of others, acquiescence of others in the industry that the patent is valid, and unexpected results. *See Graham v. John Deere Co.*, 383 U.S. 86 S.Ct. 684, 694 (1966).

A party seeking to challenge the validity of a patent based on obviousness must demonstrate by "clear and convincing evidence" that the invention described in the patent would have been obvious to a person of ordinary skill in the art at the time the invention was made. *Cubist Pharmaceuticals, Inc. v. Hospira, Inc.*, 75 F.Supp.3d 641, 663 (D.Del.2014).

Perfecting Priority

Priority and its issues of conception and reduction to practice are questions of law predicated on subsidiary factual findings. *Cooper v. Goldfarb,* 154 F.3d 1321, 1327 (Fed.Cir.1998).

More recently, the Federal Circuit noted the applicant must show he was in possession of the later claimed invention before the effective date of the reference in order to perfect priority. The Federal Circuit stated:

> "When the issue of priority concerns the antedating of a reference, the applicant is required to demonstrate, with sufficient documentation, that the applicant was in possession of the later-claimed invention before the effective date of the reference. Demonstration of such priority requires documentary support, from which factual findings and inferences are drawn, in application of the rules and law of conception, reduction to practice, and diligence."

In re Steed, 802 F.3d 1311, 1316 (Fed.Cir.2015). The purpose is to determine "whether the applicant was in possession of the claimed invention sufficiently to overcome the teachings and effect of an earlier publication of otherwise invalidating weight." *Id.*, 802 F.3d at 1316. Priority of a claimed invention therefore depends upon conception and reduction to practice. *Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1376 (Fed. Cir. 1986); *Price v. Symsek,* 988 F.2d 1187, 1190 (Fed. Cir. 1993).

ANALYSIS

I.

Here, Actavis, bears the burden of proving by clear and convincing evidence that the asserted claims 11 and 12 of the '151 patent are invalid. Actavis advances the position that claim 11 is invalid because it is inherently anticipated by the EP '938 reference, and claim 12 is

inherently obvious in view of the EP ’938 reference. However, Actavis’ invalidity defenses stand only if the EP ’938 reference is in fact a prior art reference.

The EP ’938 reference is a prior art reference to the ’151 patent under pre-AIA 35 U.S.C. § 102(a) if the invention recited in claims 11 and 12 was “patented or described in a printed publication in this or a foreign country, before *the invention* thereof by the applicant for patent.” *See* prior law or pre-AIA 35 U.S.C. § 102(a). The claimed ‘invention’ depends upon conception and reduction to practice. *Hybritech Inc.*, 802 F.2d at 1376; *see also Perfect Surgical Techniques, Inc. v. Olympus Am., Inc.*, 841 F.3d 1004, 1015 (Fed Cir. 2016).

A pre-AIA 35 U.S.C. § 102(a) reference, unlike a pre-AIA 35 U.S.C. § 102(b) reference, can be antedated, and thereby render the reference not a prior art reference. (*See* MPEP 715 “Swearing Behind a Reference – Affidavit or Declaration under 37 C.F.R. 1.131(a)”[9]); *see also In re Steed*, 802 F.3d at 1316.

In the instant matter, Merck argued that the EP ’938 reference is not prior art because the inventive concepts recited in claims 11 and 12 of the ’151 patent were conceived and diligently reduced to practice on April 14, 1993, which is prior to the publication of the EP ’938 reference (May 5, 1993). Consequently, rendering Actavis’ defenses futile. *See* Pl.’s FoF at ¶ 21[10]. Accordingly, the Court now determines whether the earliest filing date of the ’151 patent, December 21, 1993, can be perfected back to April 14, 1993.

[9] *See* MPEP 715—“To antedate a reference or activity that qualifies as prior art under pre-AIA 35 U.S.C. § 102(a) and not under pre-AIA 35 U.S.C. § 102(b), e.g., where the prior art date under pre-AIA 35 U.S.C. § 102(a) of the patent, the publication or activity used to reject the claim(s) is less than 1 year prior to applicant’s or patent owner’s effective filing date.

[10] At this reference, Merck argued that since “Actavis’s inherent anticipation and obviousness defenses are based on its contention that EP ‘938 is prior art, both of Actavis’s defenses fail if the Court finds that EP ‘938 is not prior art, and the Court need not address any other issue.”

II.

The parties agree that the subject matter of claims 11 and 12 of the '151 patent is sufficiently supported by the earlier filing date of the PCT application filed on December 20, 1994; and the U.S. patent application '083, filed on December 21, 1993, pursuant to MPEP 211.05(B).[11] (*See generally* JX 2; JX 2.0023-26; JX 2.0054-58; JX 2.0090-91; JX 3; JX 3.0023-26; JX 3.0056).

For the Court to determine that the claimed subject matter of claims 11 and 12 antedates the EP '938 reference, a pre-AIA 35 U.S.C. § 102(a) reference, Merck has the burden to show that the inventive concepts directed to posaconazole, as recited in claim 11, and the pharmaceutical composition, recited in claim 12, were in-fact—(i) conceived prior to the publication date the EP '938 reference, and (ii) diligently reduced to practice soon thereafter. *In re Steed*, 802 F.3d at 1316; *see also Mahurkar v. C.R. Bard*, 79 F.3d 1572, 1576-77 (Fed. Cir. 1996). With respect to 'conception,' only those inventions conceived are granted patent protection that are directed to patent eligible subject matter. *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S.Ct. 2347, 2350 (2014).

A. PATENTABILITY & CONCEPTION

It is important to note the interplay between patentability and invention. Under the U.S. patent laws, only those inventions are patentable, or granted patent protection, that are directed to,

[11] *See* MPEP 211.05(B): Sufficiency of Disclosure in Prior-Filed Application. Claiming the Benefit of Nonprovisional Applications ("A continuation-in-part application may include matter not disclosed in the prior-filed application. See MPEP § 201.08. Only the claims of the continuation-in-part application that are disclosed in the manner provided by 35 U.S.C. 112(a) in the prior-filed application are entitled to the benefit of the filing date of the prior-filed application. If there is a continuous chain of copending nonprovisional applications, each copending application must disclose the claimed invention of the later-filed application in the manner provided by 35 U.S.C. 112(a) in order for the later-filed application to be entitled to the benefit of the earliest filing date.").

"any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof."[12]

"Conception is the touchstone of inventorship," and it is the "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention as it is hereafter to be applied in practice." *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223 (Fed.Cir.1994). An inventor conceives of an invention upon formation of "a definite and permanent idea of the complete and operative invention." *Hybritech*, 802 F.2d at 1376.

Establishing conception requires evidence that the inventor actually made the invention and understood the invention to have the features that comprise the inventive subject matter at issue. *Invitrogen,Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052, 1064 (Fed. Cir. 2005). That is, the inventor must form a definite and permanent idea of the complete and operable invention to establish conception. *Bosies v. Benedict*, 27 F.3d 539, 543 (Fed. Cir. 1994).

Generally, for conception, the inventor must have a specific idea, or particular solution firmly in mind; however, chemical compounds have an even more stringent conception rule. For example, in one case, the Federal Circuit divided conception for chemical compounds into two parts—(i) the idea of a structure or formula of the chemical compound; and (ii) the possession of an operative method of making or synthesizing the same. *Oka v. Yousefeyh*, 849 F.2d 581, 583 (Fed. Cir. 1988) (internal citations omitted); *see also Fina Oil & Chem. Co. v. Ewen*, 123 F.3d 1466, 1473 (Fed.Cir.1997); *Falana v. Kent State Univ.*, 669 F.3d 1349, 1357 (Fed. Cir. 2012)

[12] At first glance, the observation of a metabolite in the mouse may be a natural phenomenon that is not subject to patentability; but neither party argued same. It appears the synthesizing of the compound and developing it into a useful product is patentable. *Molecular Pathology v. Myriad Genetics, Inc.*, 133 S.Ct. 2107, 2116 (2013).

("Conception of a chemical compound requires knowledge of both the specific chemical structure of the compound and an operative method of making it.").

"*The idea of a structure or formula of the chemical compound*"

In *Oka*, the Federal Circuit cited to *Townsend v. Smith*, 36 F.2d 292, 295 (CCPA[13] 1929) to further elaborate on this two prong test to determine 'conception.' The Court noted that the first prong is "'the directing conception' and may be defined as the idea or conception that a certain desired result may be obtained by following a particular general plan. The directing conception is often referred to as the inventive concept, thought or idea." *Oka*, 849 F.2d at 583. That is, "[c]onception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it." *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991).

On April 14, 1993, Dr. Pramanik configured the chemical structure in his notebook of Metabolite A after reviewing the mass spectra provided by mass spectrometrist Dr. Heimark. (*See* JX 7.0001; *see also* Part D of the Introduction Section). In his configuration of the chemical structure (SCH 51048 Metabolite), Dr. Pramanik provided substantial detail and specificity of the SCH 51048 metabolite. That is, Dr. Pramanik drew out—(i) all the components of the azole core, (ii) all the components of the piperazine linker, (iii) all the components of a side chain; and (iv) where the side chain is attached to the piperazine linker.

In the azole core and the piperazine linker, Dr. Pramanik was specific with respect to the bonds (single or double bonds) between the different chemical elements (i.e., Nitrogen (N), Fluorine (F), Oxygen (O), Hydrogen (H), and Carbon (C)) that formed the azole core and the

[13] CCPA refers to the former Court (U.S. Court of Customs and Patent Appeals) which was reconstituted into the United States Court of Appeals for the Federal Circuit. 96 Stat. 25 (1982).

piperazine linker. Additionally, he unambiguously noted the bond orientation; drawing dashed lines in the azole core to represent accurate three-dimensional configuration. The dashed lines depict bonds extending toward the reader, and the solid wedge-shaped lines depict bonds extending away from the reader. (*See* Def.'s Br. at 4-5; D.I. 162). And, lastly, with respect to the hydroxyl group, OH, in the side chain, he was specific to connect it to a particular location of the piperazine linker.

Dr. Pramanik discussed his findings with Drs. Giri and Saksena the very same day, April 14, 1993. In this meeting, it was determined that there are seven possibilities for the chemical structure, which included two primary alcohols, four secondary alcohols, and one tertiary alcohol. (*See* Pl.'s FoF at ¶¶ 121-124). The tertiary alcohol was quickly ruled out during this meeting, and they collectively decided to synthesize and test each of the six alcohols to determine which one of the six had antifungal activity. (*See* Pl.'s FoF at ¶ 127; *citing* Trans. at 476:13-20 (Saksena); 1145:21—1146:2 (Giri); and 1337:25—1338:2 (Glick)).

During this meeting on April 14, 1993, Drs. Giri and Saksena (inventors of the '151 patent) had conceived of the chemical structure or formula of a potential antifungal drug that would result in posaconazole. In other words, Schering perceived that the OH, or hydroxyl group, was included in the side chain that was attached to the piperazine linker. And, wherein one of the six possible configurations constituted the chemical structure of posaconazole. (*See* Pl.'s FoF at ¶ 180). All that was required hereon was to perform testing to determine which stereoisomer would provide activity against fungal agents, both *in vivo* and *in vitro,* and thereby be developed into a marketable drug.

Moreover, Actavis agrees that the structure of posaconazole was conceived on April 14, 1993. (*See* Def.'s FoF at ¶ 23 (*citing* Trans. at 412:7-10 (Pramanik); "[t]here is no dispute that it

was Dr. Pramanik, not named inventors Dr. Saksena or Dr. Giri, who first *conceived of the structure of posaconazole*"); *see also* Def.'s Br. at 4-5)[14]. Accordingly, the Court finds that the chemical structure or formula of the chemical compound posaconazole, was perceived on April 14, 1993 as memorialized in Dr. Pramanik's lab notebook.

In *Oka*, the Federal Circuit, again citing to *Townsend*, noted that the second part of conception is "the selection of the means for effectively carrying out the directing conception." *Oka*, 849 F.2d at 583. That is, the inventor must show it had an operative method of making or synthesizing the compound. The Court noted that when "a method of making a compound with conventional techniques is a matter of routine knowledge among those skilled in the art, [in which case] the compound has been deemed to have been conceived when it was described, and the question of whether the conceiver was in possession of a method of making it is simply not raised." *Id.*; *see also Burroughs Wellcome Co.*, 40 F.3d at 1230.

In other words, 'operable route' can be shown by satisfying either an objective standard or a subjective standard. The subjective standard requires a showing of independent, corroborated evidence that the inventors actually possessed an operative method of making the chemical compound. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1171-72 (Fed. Cir. 2006). Whereas, the objective standard requires a showing of evidence that "a method of making the compound with conventional techniques [was] a matter of routine knowledge among those skilled in the art." *Oka*, 849 F.2d at 583-84; *see also* Def.'s Reply at ¶¶ 12-30; Pl.'s Reply at ¶¶ 12-33). From a review of the evidence, the Court finds that Merck has shown the subjective standard has been met[15].

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[14] The argument of improper inventorship of the '151 patent pursuant to pre-AIA 35 U.S.C. § 102(f) is not raised as a defense in the invalidity contentions.

[15] Where there is no corroborated evidence one can demonstrate that the inventor actually possessed an operative route to produce a compound, by showing that "method of making a compound with

With respect to the subjective standard, because conception is a mental act, courts require corroborating evidence, such as contemporaneous documentation testimony, which would enable a POSA to make the invention. *Burroughs Wellcome*, 40 F.3d at 1228.

The requirement of independent knowledge remains key to the corroboration inquiry, and such corroboration "must not depend solely on the inventor himself." *See Reese v. Hurst*, 661 F.2d 1222, 1225 (CCPA 1981). "Independent corroboration may consist of testimony of a witness, other than the inventor, to the actual reduction to practice or it may consist of evidence of surrounding facts and circumstances independent of information received from the inventor." *Id.* One consequence of the independence requirement is that the testimony of one co-inventor cannot be used to help corroborate the testimony of another. *Lacks Indus. v. McKechnie Vehicle Components USA, Inc.*, 322 F.3d 1335, 1350 (Fed. Cir. 2003).

Nevertheless, "[t]he law does not impose an impossible standard of 'independence' on corroborative evidence by requiring that every point of a reduction to practice be corroborated by evidence having a source totally independent of the inventor...." *Cooper v. Goldfarb*, 154 F.3d 1321, 1330 (Fed. Cir. 1998) (internal quotations omitted). Similarly, "it is not necessary to produce

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conventional techniques is a matter of routine knowledge among those skilled in the art." Oka, 849 F.2d at 583. This is an objective test that looks to the knowledge of "those skilled in the art"—i.e., public information available to POSA. Creative Compounds, LLC v. Starmark Labs., 651 F.3d 1303, 1312-13 (Fed. Cir. 2011); Falana v. Kent State Univ., 669 F.3d 1349, 1358 (Fed. Cir. 2012) (equating the "routine" nature of a synthesis with the "basic exercise of normal skill expected of one skilled in the art").

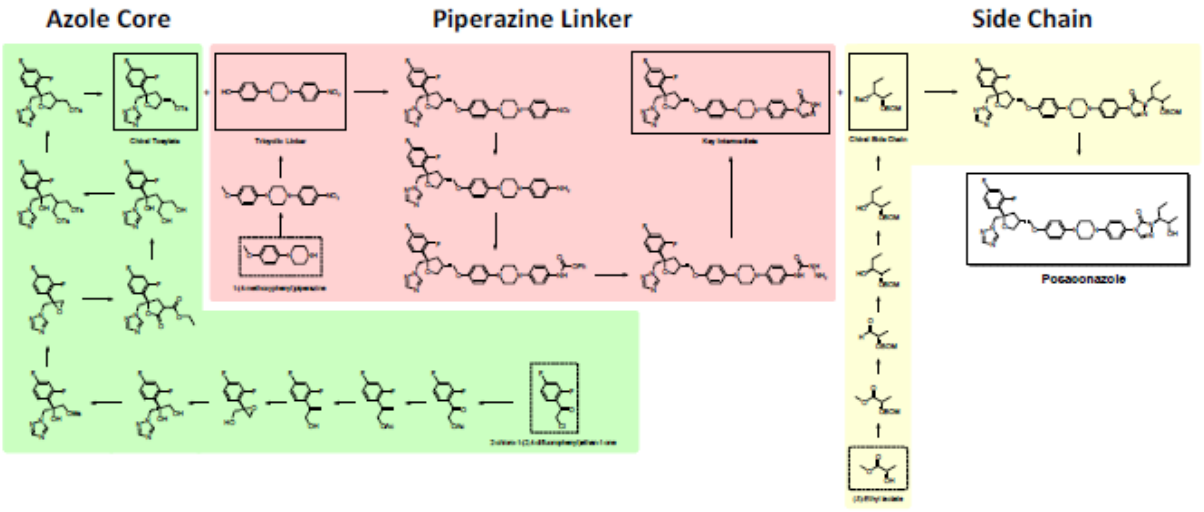
Merck attempts to show same by arguing a POSA would have had the knowledge to make posaconazole, in particular posaconazole's azole core. (See Pl.'s FoF at ¶ 169; see also Def.'s FoF at ¶ 46 (citing Trans. at 702:19—703:2 (Dolle) ("A [POSA] would have known how to synthesize that left hand piece […] That is the basis of a patent by Schering-Plough a couple of years earlier, I believe we referred to it here as the '676 patent."); see also Trans. at 705:21-25 (Dolle) ("The piperazine core was well-known in the prior art [in 1993].").

Here, the Court refrains from delving into the objective inquiry as to whether "method of making a compound with conventional techniques is a matter of routine knowledge among those skilled in the art." Oka, 849 F.2d at 583. Merck's burden was to satisfy either the objective standard or the subjective standard. Id.; see also Medichem, S.A., 437 F.3d at 1171-72. As discussed herein, there is sufficient independent, corroborating evidence showing that the inventors of the '151 patent actually possessed an operative method of making the subject matter of claims 11 and 12.

an actual over-the-shoulder observer. Rather, sufficient circumstantial evidence of an independent nature can satisfy the corroboration requirement." *Id.*

Here, Actavis argues that Merck has presented no corroborated evidence that the inventors actually possessed an operative method of synthesizing posaconazole on April 14, 1993. In a nutshell, Actavis argues the following—(i) testimony of inventors Drs. Giri and Saksena is insufficient as a matter of law to support its contention that inventors actually possessed an operable method of making posaconazole. (*see* Def.'s Reply at ¶ 26); (ii) the synthesis contemplated by the inventors on April 14, 1993, was of SCH-55801 (a racemic mixture), and not posaconazole itself—the subject matter of claim 11 (*id.* at ¶ 28); (iii) Dr. Bennett, and not Mr. Lovey, performed the first synthesis of posaconazole in August 1993 (*id.* at ¶ 29); (iv) prosecution history of the '151 patent dictates that the inventors limited the claim scope of claim 11 to a specific compound with specific stereochemistry, i.e., the single posaconazole stereoisomer (*id.* at ¶ 30); and (v) the racemic mixtures made by Mr. Lovey did not contain any posaconazole, as testified by Mr. Lovey on one occasion, but who testified differently on another. (*id.* at ¶ 31).

Actavis provides Dr. Glick's testimony that more than routine skill and conventional techniques are required to synthesize posaconazole. (*See* Def.'s FoF at ¶ 37 (*citing* Trans. at 511:23—512:12 (Saksena); 1302:24—1303:22 (Glick)). Dr. Glick testified that posaconazole is a large, complex molecule, which is further complicated by the presence of four stereocenters. And because of its size and complexity, the synthesizing of posaconazole requires twenty-six (26) separate chemical reactions, as shown below—



(*Id.* at ¶ 38).

Dr. Glick further testified that it took Schering scientists years of experimental work, and numerous failures, before they could configure out a way to synthesize the posaconazole compound. (*Id.* at ¶ 39). One part that was particularly challenging was synthesizing the azole core ("28R"), which contained the weakest step in the entire sequence because the problems with synthesizing the azole core just did not go away. (*Id.* at ¶ 40 (*citing* "Schering's President's Award for Scientific/Technical Achievement" (the "Nomination Memo") (JX 44.0016-18)).

The Nomination Memo seeks an internal Schering award for the work that the Schering scientists did in the antifungal program for over a decade, starting in the 1980s with their synthesis of analogs based on ketoconazole, to their development of the tetrahydrafuran family of triazole compounds in the early 1990s. (*See* Pl.'s FoF at ¶ 145). Prior to May 5, 1993, the chemistry that Schering had developed, which is described in the Nomination Memo, had not been published and not available to a POSA on April 14, 1993. (*See* Def.'s FoF at ¶ 42).

With respect to the side chain, Dr. Glick testified that making the side chain and attaching the same to the piperazine linker would have been much easier, and even routine, for a POSA. (*Id.* at ¶ 48 (*citing* Trans. at 1304:19—1305:2, 1305:12—1306:14, 1309:12-14)).

In opposition, Merck contends that Dr. Giri, Dr. Saksena, and Mr. Lovey had extensive experience working on related antifungal compounds, including ones with an azole core and piperazine links prior to April 14, 1993, as they were skilled chemists. (*See* Pl.'s FoF at ¶¶ 136-137). Antifungal compounds that included an azole core and a piperazine linker. In support, Merck relies on Dr. Giri's testimony which is corroborated by *internal* Schering documents (i.e., the Nomination Memo), and Dr. Giri's history of working on compounds like posaconazole. (*Id.* at ¶ 144).

Merck purports that when the inventors of the '151 patent conceived the structure of posaconazole on April 14, 1993, they already knew how to make SCH-51048, since they disclosed the same on October 28, 1992 (filing date of the EP '938 reference), and they had extensive experience working on similar compounds. (*Id.* at ¶¶ 136-137). The EP '938 reference is a contemporaneous disclosure corroborating that the inventors knew how to make the azole core and the piperazine linker. The lack of publication of the EP '938 reference is immaterial to inventor's state of mind.

The Court finds Merck's arguments persuasive that on April 14, 1993, there was substantial corroborating evidence, such as contemporaneous documentation and testimony, to show that the inventors of the '151 patent had an 'operable route' to synthesizing posaconazole.

The inventors of the '151 patent already knew how to make the azole core and piperazine linker as of April 14, 1993. This is evidenced by the fact that—(i) Compound IIc or SCH-51048 and posaconazole of the '151 patent have the same azole core and piperazine linker, the two most complicated components of posaconazole as testified by Dr. Glick, (ii) the EP '938 reference shares the same inventors as the '151 patent (i.e., Dr. Saksena, Ashit Ganguly and Mr. Lovey), although different inventive entity, which was assigned to Schering; and (iii) the EP '938 reference

discloses how to synthesize the azole core and the piperazine linker. (*See* Pl.'s FoF at ¶¶ 135-138). That is, the fact that Schering scientists experimented with drugs involving antifungal drugs for number of years, shows strong corroborating evidence that the inventors of the '151 patent had the knowledge, familiarity and understanding to synthesize the azole core and the piperazine linker prior to the filing of the EP '938 reference in 1992. Combining this with the years of experimental work by Schering, there is substantial corroborative evidence that inventors of the '151 patent had the operative route or method of making posaconazole on April 14, 1993. Moreover, Schering scientists had the knowledge of such synthesis for years, but it may not have become available to the rest of the scientific community until May 5, 1993 (the publication date of the EP '938 reference).

The years of work done by Schering in developing antifungal drugs is evidenced by the Nomination memo. This memo shows that Dr. Giri, Dr. Saksena, and Mr. Lovey, among others, were familiar with the synthesis of the azole core and the piperazine linker, as they had made them during the course of the antifungal program. (*See* Pl.'s FoF at ¶ 145).

The Nomination memo addresses the problems with conventional drugs for treating antifungal activity, and what were the objectives of achieving a novel antifungal agent with broad-spectrum activity. (*See* JX 44.0002-0004). Further, the memo notes that, interestingly, SCH-51048 was found to be more active *in vivo* than its counterpart analog. Consequently, existing efforts were redirected in support of SCH-51048. (*Id.* at 44.0017-18).

Schering scientists experienced synthetic problems in formulating SCH-51048, which required an extremely challenging and novel chemistry to make the azole core ("28R"). (*Id.*). And, because no examples existed in the literature for formulating the same, Schering scientists undertook two approaches. The first approach was not promising; however, the second approach

was ‘close to a breakthrough’ (*Id.* at 44.0020). The second approach required numerous chemical reactions, as outlined in Schemes VII & VIII, to achieve the desired chemical structure. (*Id.* at 44.22-25). The memo concludes by stating the following—

> “We have described here a significant effort leading to the discovery of Sch 51048, a potent antifungal agent in advanced stages of preclinical development. Its excellent broad spectrum activity (P.O.) and superiority over most existing (synthetic) antifungal agents has been confirmed by our outside investigators. Sch 51048 is by far the best compound in the prophylactic treatment protocol against *Candida* infection model. We believe this has placed Schering-Plough well ahead of our competition.”

(*Id.* at 44.0034).

The Nomination memo provides corroborative evidence to Dr. Giri’s testimony that he, and other Schering scientists, knew how to synthesize the six alcohols, including posaconazole, on April 14, 1993. Furthermore, having this knowledge in hand, Drs. Giri and Saksena were able to direct Mr. Lovey with the synthetic steps to make the racemates or racemic mixtures. As discussed above, Mr. Lovey’s five-step synthesis of SCH-55801, which started on April 26, 1993 and completed by May 26, 1993, included—(i) dihydroxylation of 2-pentene (step 1); (ii) protection of 2,3-pentanediol (step 2); (iii) sulfonation of SEM protected 2,3 pentanediol (step 3); (iv) coupling of triazole core (step 4); and (v) deprotection to remove SEM protecting group, yielding posaconazole and its enantiomer (step 5). (*See* PX 1010; Pl.’s FoF at ¶ 182-183).

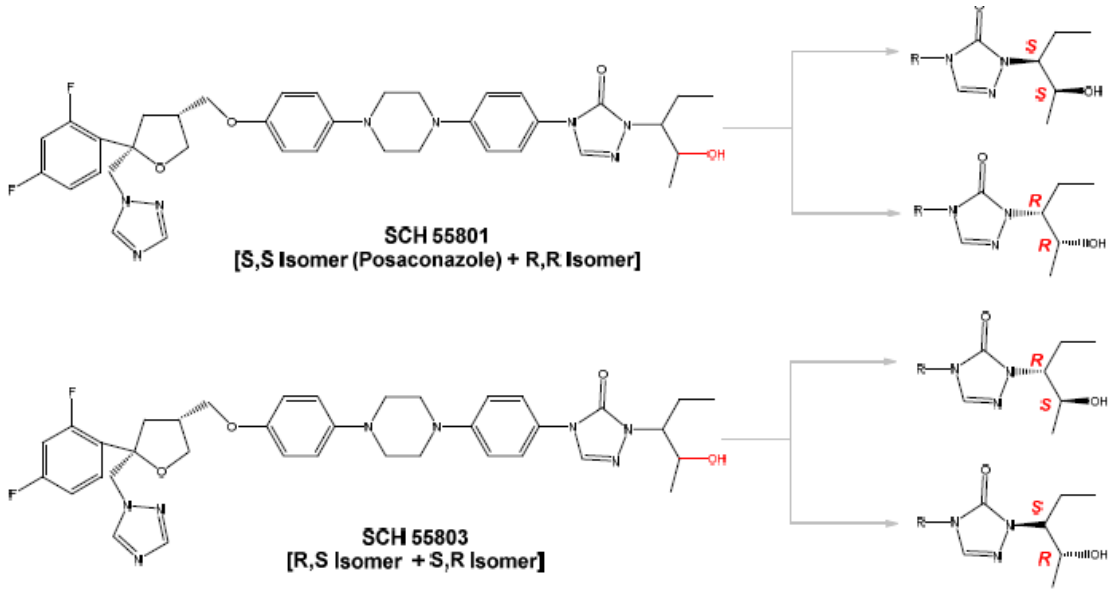
Dr. Giri, Dr. Saksena, and Mr. Lovey had the general plan or the operable route in hand that constituted the method of making posaconazole. However, Actavis raises an interesting argument that what Mr. Lovey synthesized on May 26, 1993, is not posaconazole, the subject matter of claim 11. Instead, Mr. Lovey’s synthesis was a racemic mixture, which did not include *pure* posaconazole, the subject matter of claim 11. (*See* Def.’s Reply at ¶¶ 23-24).

Actavis also notes that Mr. Lovey stated in one of his depositions that he did not make posaconazole, but in other depositions he noted that he had posaconazole in a racemic mixture. Further, in support of its argument, Actavis cites to the inventors' statements made during the prosecution of the '151 patent, where inventors stated that claim 11 may cover the single stereoisomer posaconazole and not a racemic mixture containing posaconazole and one or more other stereoisomers. (*Id.* at ¶ 24; *citing* DTX-27_205). However, Actavis does not dispute that Mr. Lovey was asked to make posaconazole as a 1:1 mixture with the R,R isomer (i.e., SCH-55801). (*See* Pl.'s Reply at ¶ 18 (*citing* Def.'s FoF at ¶ 26)).

Merck agrees that in the course of making this amendment, the applicants stated that the claims have been amended "to cover a specific compound with specific stereochemistry." (*See* Pl.'s Reply at ¶ 33; *citing* DTX 27_025). However, Merck notes that claim 11 does not restrict the claim to posaconazole in a pure form. And, as such, a racemic mixture that contains posaconazole could potentially read on claim 11. (*Id.* at ¶ 33).

Actavis' argument that claim 11 is directed to 'pure' posaconazole, and in turn avoids a racemic mixture that includes posaconazole is unpersuasive. Granted, statements made by the Applicant to the Patent Office characterizing his or her invention may give rise to prosecution disclaimer, which is part of the intrinsic evidence. *Hockerson-Halberstadt, Inc. v. Avia Group Int'l, Inc.*, 222 F.3d 951, 957 (Fed. Cir. 2000); *see also Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005). However, here, fair reading of the statement does not limit scope of claim 11 to only 'pure' posaconazole. Moreover, and more importantly, the corroborative evidence of the contemporaneous disclosure of the EP '938 reference indicating the inventors knew how to make the azole core and the piperazine linker, demonstrates that specific instructions on how to synthesize the different alcohols was within the minds of the inventors on April 14, 1993.

Applicants' statement that the amended claim 11 "covers a specific compound with specific stereochemistry," does not exclude a racemic mixture, such as SCH-55801, because such formulation includes a specific compound (i.e., posaconazole and an isomer) with specific stereochemistry (i.e., S,S and R,R). As shown below, SCH-55801 has a specific compound and specific stereochemistry that is different from the other racemic mixtures such as SCH-55803, for example.



(*See* Pl.'s FoF at ¶ 180). As such, the Court notes that claim 11 covers both, a pure posaconazole compound and a racemic mixture that includes posaconazole.

Accordingly, based on the foregoing reasons, the Court is satisfied that Merck met its burden of producing independent, corroborated evidence, which shows that the inventors of the '151 patent actually possessed an operative method of making the subject matter recited in claims 11 and 12.

Accordingly, the Court finds that Merck has satisfied the subjective inquiry by showing that there was independent, corroborating evidence available to the inventors on April 14, 1993,

such that they had an 'operable route' or method of synthesizing posaconazole and a pharmaceutical composition containing the same.

In conclusion, with respect to the 'conception' inquiry, the Court finds that the inventors of the '151 patent—(i) had the idea of a structure or formula of posaconazole and pharmaceutical composition containing the same on April 14, 1993, and (ii) the possession of an operative method of making or synthesizing the same was also present on April 14, 1993.

B. DILIGENTLY REDUCING TO PRACTICE

i. REDUCTION TO PRACTICE

There are two types of reduction to practice—(i) constructively, by filing a patent application; and (ii) actually, by building and testing a physical embodiment of the invention. If the inventor relies on a constructive reduction to practice, the filed application must fully disclose the invention. *Travis v. Baker*, 137 F.3d 109, 111 (CCPA 1943); *Hybritech*, 802 F.2d 1367, 1376 (Fed. Cir. 1986). Whereas, an actual reduction to practice must show that the invention works for its intended purpose in the actual environment of its use. *Scott v. Finney*, 34 F.3d 1058, 1062 (Fed. Cir. 1994).

In *Scott*, the Court explained:

> "the testing requirement depends on the facts of each case, with the court guided by a common sense approach in weighing the sufficiency of the testing. Reduction to practice does not require that the invention, when tested, be in a commercially satisfactory stage of development. Testing need not show utility beyond a possibility of failure, but only utility beyond a probability of failure. When reviewing the sufficiency of evidence of reduction to practice, this court applies a reasonableness standard."

Scott, 34 F.3d at 1061-62 (quotations and citations omitted).

On some occasions conception and reduction to practice occur simultaneously. *Alpert v. Slatin*, 305 F.2d 891, 894 (CCPA 1962); *Amgen, Inc.*, 927 F.2d at 1207. "[I]n some unpredictable

areas of chemistry and biology, there is no conception until the invention has been reduced to practice." *MacMillan v. Moffett*, 432 F.2d 1237, 1234-40, 167 USPQ 550, 552-553 (CCPA 1970).

Here, the constructive reduction to practice of the subject matter recited in claims 11 and 12 was accomplished on December 21, 1993, the filing date of the earliest parent application from which the patent application of the '151 patent claims priority. As such, the constructive reduction to practice took place on December 21, 1993.

Whereas actual reduction to practice of claim 11 took place on April 14, 1993, when inventors of the '151 patent discovered the hydroxyl or OH group on the side chain of metabolite A. This hydroxyl group was missing from the parent compound, Compound IIc or SCH 51048. The Court finds that the reduction to practice of posaconazole was envisioned on April 14, 1993, but some further testing and analysis was required on part of Schering's scientists to determine and confirm which one of the six alcohols had adequate antifungal activity such that it could be commercially used. Although such further testing and analysis is not a requirement for showing actual reduction to practice. (*Scott*, 34 F.3d at 1061-62). It was a prudent practice to confirm same through more in depth analysis.

Accordingly, the Court finds that the subject matter recited in claim 11 was actually reduced to practice on April 14, 1993.

With respect to claim 12, which depends from claim 11, it requires a pharmaceutical composition comprising an antifungally effective amount of the posaconazole compound of claim 11 with a pharmaceutically acceptable carrier. In the *Markman* opinion, the Court defined "pharmaceutical composition" to mean—"formulation of at least one active ingredient with a substance or collection of substances capable of being combined with the at least one active ingredient;" and "pharmaceutically acceptable carrier" to mean—"substance or collection of

substances capable of being combined with an active ingredient that is suitable for use in contact with the tissues of mammals for purposes of a therapeutic treatment in the mammals under anticipated exposure conditions." (*See* Memorandum & Order at p. 19; D.I. 164) As such, the subject matter of claim 12 requires that the composition consisting of posaconazole is suitable for use in contact with the tissues of mammals in order to provide a therapeutic treatment in the mammals under anticipated exposure conditions.

Since the inventors of the '151 patent were not certain that the posaconazole compound conceived on April 14, 1993, can be used for its intended purpose in the actual environment of its use, which is for treating antifungal activity and commercializing the same, further testing and analysis was required. *Scott*, 34 F.3d 1058.

It is necessary to decide when the actual reduction to practice occurred. The Court finds that on April 14, 1993, Mr. Lovey was tasked by Dr. Giri and Dr. Saksena to synthesize the *racemic* mixture containing posaconazole and its corresponding (R,R) stereoisomer. (*See* Def.'s FoF at ¶ 26). Mr. Lovey employed a five-step synthesis of SCH-55801 starting on April 26, 1993, and completed the work by May 26, 1993. With respect to synthesizing *pure* posaconazole compound, SCH-56592, Dr. Bennett began his synthesis of pure posaconazole on June 30, 1993, and completed the synthesis on August 20, 1993. (Pl.'s FoF at ¶¶ 161-164).

Since claim 11, which is incorporated in claim 12, applies to both—(i) a racemic mixture that contains posaconazole; and (ii) pure posaconazole—both dates, May 26, 1993 and August 20, 1993, apply as to the actual reduction to practice of the subject matter recited in claim 12.

The Court recognizes that the aforementioned two dates occur after the publication date of the EP '938 reference (May 5, 1993). Merck has shown by substantial evidence that prior to the May 5, 1993 publication date of the EP '938 reference, that the reduction to practice at a later date

is coupled with due diligence (discussed below) from the conception date of April 14, 1993. (*See* MPEP 715 "Swearing Behind a Reference – Affidavit or Declaration under 37 CFR 1.131(a). *See also Rieser v. Williams*, 225 F.2d 419, 423 (CCPA 1958)

Accordingly, the Court determines that the subject matter recited in claim 12 was actually reduced to practice on May 26, 1993 and August 20, 1993.

ii. DILIGENCE

While diligence naturally depends on the factual circumstances, it requires persistent work from conception to reduction to practice. The diligence relates to reasonable "attorney-diligence" and "engineering-diligence." *Keizer v. Bradley*, 270 F.2d 396, 397 (CCPA 1959). Once the invention has been conceived, the patent holder must show reasonable diligence from just prior to the competing reference's effective date until the date of the invention's reduction to practice. *Perfect Surgical*, 841 F.3d at 1007 (*citing Monsanto Co. v. Mycogen Plant Sci., Inc.*, 261 F.3d 1356, 1363 (Fed. Cir. 2001)). "The party chargeable with diligence must account for the entire period during which diligence is required." *Gould v. Schawlow*, 363 F.2d 908 (CCPA 1966) (Merely stating that there were no weeks or months that the invention was not worked on is not enough).

Here, with respect to claim 11, diligence is not an issue because posaconazole was conceived and simultaneously reduced to practice on April 14, 1993. Whereas, with respect to claim 12, the Court finds that Schering was diligent in reducing to practice the subject matter of claim 12. Based on the evidence presented before the Court, there were no gaps in the record that would allow one to question diligence on part of the inventors of the '151 patent.

For example, Mr. Lovey's five-step synthesis of SCH 55801 started on April 26, 1993, and was completed by May 26, 1993. (*See* Pl.'s FoF at ¶ 154). Similarly, Dr. Bennett began his

synthesis of pure posaconazole on June 30, 1993, and completed the synthesis on August 20, 1993. (*Id.* at ¶ 161).

Actavis raises concerns that inventors of the ’151 patent were not diligent because they were not focused specifically on posaconazole. Instead, the inventors were simply just concerned about synthesizing and testing numerous compounds, which did not include posaconazole. (Def.’s FoF at ¶¶ 48-50). The Court does not find Actavis’ arguments persuasive because by its own admission it agrees that Dr. Pramanik identified posaconazole as a potential active metabolite of SCH 51048. (*See* Def.’s Br. at 4-5). This was taken under consideration by Dr. Giri and Dr. Saksena, senior chemists in charge of the antifungal program, who immediately delegated tasks to Mr. Lovey to synthesize the racemic mixtures. (Def.’s FoF at ¶¶ 25-26). From thereon out, Mr. Lovey synthesized racemic mixtures on May 26, 1993, and Dr. Bennett’s synthesis of pure posaconazole on June 30, 1993. Merck has shown that reasonable diligence was undertaken from the date of conception, April 14, 1993, to reduction to practice—May 26, 1993 (racemic mixtures) and August 20, 1993 (pure posaconazole).

Accordingly, the Court determines that the inventors of the ’151 patent were diligent in reducing to practice the subject matter recited in claim 12.

III.

The Court finds that Merck has successfully met its burden in establishing that the inventors of the ’151 patent conceived the subject matter recited in claims 11 and 12 on April 14, 1993, and diligently reduced the inventions to practice soon thereafter.

Because the EP ’9387 reference is a pre-AIA 35 U.S.C. § 102(a) reference, and not a § 102(b) reference, Merck can successfully antedate this reference and render it not a prior art

reference. *See In re Steed*, 802 F.3d at 1316; *see also* MPEP 715 "Swearing Behind a Reference – Affidavit or Declaration under 37 C.F.R. 1.131(a)."

As such, since the Court finds that Merck can successfully antedate the EP '938 reference, Actavis' both invalidity contentions—(i) inherent anticipation under pre-AIA 35 U.S.C. § 102(a) with respect to claim 11; and (ii) obviousness under pre-AIA 35 U.S.C. § 103(a) with respect to claim 12, lack merit.

ORDER

IT IS on this 28th day of September, 2017,

ORDERED that claim 11 of the 5,661,151 ("the '151 patent") patent is not invalid under pre-AIA 35 U.S.C. § 102(a); and it is further

ORDERED that claim 12 of the '151 patent is not invalid under pre-AIA 35 U.S.C. § 103(a).

s/Peter G. Sheridan
PETER G. SHERIDAN, U.S.D.J.